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Description

This invention relates to a method and a device for injection, especially for use in ambulatory treatment. More specifically, the invention relates to a method and a device by means of which an injection solution of a substance is prepared immediately before the injection, or in the preparation of several doses, before the first injection.

Injection devices for use in ambulatory treatment where the medicament is present in a solution are previously known and have been widely used in, for example, insuline treatment of diabetes. Such devices are usually built so that the patient himself can easily assemble a cylinder ampoule for one or more doses, an injection needle and a dosing device in a suitable holder and thereafter give himself easily the required injection. In the device it is also easy to exchange used ampoules and needles for new ones. In an assembled state, such injection devices are often shaped like a fountain-pen and can be easily brought along by the patient.

Moreover, so-called dual-chamber or mixing containers or cylinder ampoules are also known for preparation of solutions of sensitive substances immediately before the injection. Prior dual-chambers are e.g. known form US-A-2549417, US-A-2 607344, US-A-2717601, US-A-4613326, US-A-4226236 and EP-A1-0207544. All these documents disclose ampoules of the type intended to be used in the present invention. Such ampoules are divided into two chambers separated by a movable wall or piston. The sensitive medicament is present in the front chamber in a dry, usually freeze-dried state and the front end of the front chamber is sealed by a wall penetrable to an injection needle. The liquid intended to dissolve the sensitive substance before the injection is present in the rear chamber. The two chambers are separated by a front movable wall and the rear end of the rear chamber is sealed by means of a rear movable wall. Furthermore, in the container wall there is arranged a connecting passage which can connect the front and the rear chambers.

In a storage position before the injection, there is no communication between the front and the rear chambers. The inlet as well as the outlet of the connecting passage ends in the front chamber.

When the container is to be readied for injection, the rear, movable wall in the rear chamber is moved forwards, and due to the incompressibility of the liquid, the front movable wall will then also be moved forwards until it reaches a position just opposite the connecting passage in the wall of the container. When the rear movable wall thereafter is moved further forwards, the liquid will be pressed through the overflow passage into the front chamber where it will be brought into contact with the medicament and dissolve this. At the injection the two walls will act together as a piston and press the prepared injection solution out through a needle introduced through the front end wall in the front chamber.

In certain cases the medicament can be so sensitive that special measures must be taken to protect the substance against mechanical influence at the time of dissolution as well as in the further handling of the solution. This applies for example to freeze-dried growth hormones where even a simple shaking of the substance and the liquid can lead to a non-acceptable biochemical change. The readying of the container for injection must then be made with the utmost carefulness.

In prior art devices as those disclosed in US-A-2607344, US-A-1709691, US-A-4613326, US-A-4226236 and EP-A1-0207544 the mixing of the substances is obtained by manually pressing a rod against a movable end wall of an ampoule. However, as these devices when pressing the movable end wall of the ampoule forwards tend to create a shock wave when the liquid is pressed through the overflow passage, these devices cannot be used with ampoules containing substances sensitive to degradation.

US-A-4592745 discloses a dispenser which enables dispensing of accurate dosages from prefilled cartridges.

It would be very desirable to have available an injection device that is as easy to bring along and handle as those previously known for simple cylinder ampoules in which the medicament is present in a liquid stage as a solution, suspension or emulsion, at the same time as the advantages of mixing containers at injection of sensitive substances might be utilized. This object is now achieved by the present invention.

According to the invention there are provided a method and a device for preparation of an injection solution of one or more substances sensitive to degradation, and a subsequent injection of this solution.

It is intended by the method of the invention to prepare a solution, emulsion or suspension in water of one or more sensitive medicaments for one or more subsequent injections, using a multi-chamber cylinder ampoule known per se which comprises a front space containing the sensitive medicament and is sealed at its front end by means of a membrane penetrable to an injection needle and delimited at its rear end by a front movable wall, a rear space containing an aqueous phase and which is delimited at its front end by the front movable wall and is delimited at its rear end by a rear movable wall, and a connecting passage arranged in the wall of the ampoule between the rear and the front space, the rear movable wall being moved forwards and entraining thereby the aqueous phase and the front, movable wall until this is just opposite the overflow passage so that the aqueous phase upon continued forward motion of the rear movable wall will flow past the front movable wall into the front space and dissolve, emulsify or suspend the

medicament. What characterizes the method is that the rear movable wall is pushed forward into the ampoule by means of a screw mechanism while the ampoule is held in essentially vertical direction with the needle end pointing upwards so the aqueous phase is made to flow calmly from below and upwards through the medicament avoiding any shaking and admixture of air.

Moreover, the invention comprises a device for carrying out the present method, said device comprising :

a) a container for the constituents of the injection solution, in which the constituents are kept separated but can be brought together by external action to be mixed and dissolved and which is made as a tube which is sealed at its front end by means of a penetrable membrane, in a space between the penetrable wall and a front movable wall contains the solid constituents of the injection solution, in a space between the front movable wall and a rear movable wall contains the liquid constituents of the injection solution and in the tubular wall is provided with a connecting passage so arranged that when the rear movable wall is moved forwards together with the liquid and the front movable wall, the liquid can flow past the front movable wall and be mixed with the solid constituents to a solution ;

b) holder means in which the container can be fixed such that the constituents of the injection solution are brought together and mixed and which is made of two tubular members which can be screwed together and enclose the container so that when the members are screwed together the front end of the container with the penetrable membrane is exposed at the front end of the holder means to be penetrated by an injection needle and the rear movable wall at the rear end of the container is moved forwards together with the liquid and the front movable wall so that the liquid is made to flow through the connecting passage over to the space of the solid constituents, to be mixed with these to a solution ;

c) holder means for an injection needle arranged to be applied to the front end of the holder means of the container so that the needle can be to connected with the interior of the container through the penetrable membrane ; and

d) a dosing device connected to the holder means of the container, through the operation of which the rear movable wall in the container is made to be displaced forwards in a controlled way administering determined doses of the injection solution, said dosage device being brought to a starting position for dosage when the holder means of the container are screwed together.

The invention also comprises a more universally useful device for preparation of an injection solution of constituents placed in a container according to point a) above.

In the following, the invention is described in greater detail with reference to the accompanying drawing.

An embodiment of a device according to the invention is shown in the drawing. Fig. 1 in the drawing shows a dual-chambered cylinder ampoule having two chambers for use in an injection device. Fig. 2 is a general view of an injection device according to the invention and Fig. 3 shows the same device in its disassembled state. Fig. 4 is a sectional view of the device in its disassembled state and Fig. 5 shows the device ready for injection. Fig. 6 is a schematic view of a first embodied variant of the device according to the invention in a position before the preparation of the injection solution, Fig. 7 is a schematic view of the device in Fig. 6 after the preparation of the injection solution, Fig. 8 is a schematic view of the device shown in Figs. 6 and 7 when taking out the prepared solution into a hypodermic syringe. Fig. 9 is a schematic view of a second embodied variant of the device according to the invention in a position before the preparation of the injection solution. Fig. 10 is a schematic view of the device shown in Fig. 9 after the preparation of the injection solution, and Fig. 11 is a schematic view of the device according to Figs. 9 och 10 with applied cannula and ready for injection.

A sectional view of a dual-chamber cylinder ampoule for use in an injection device according to the invention is shown in Fig. 1. The ampoule consists of a tube 1, preferably of glass or a plastic material, which is formed as a bottle-neck with a flange 2 at its front end. The front end is sealed by means of a membrane 3 of rubber or a suitable plastic material which is secured by means of a metal capsule 4. The capsule 4 has an aperture 5 at its central portion so that the membrane 3 is uncovered there. The edge portion of the capsule is further bent around the flange 2 so that the membrane 3 is secured against the front aperture of the ampoule.

The ampoule is divided into a front space 6 and a rear space 7 by means of a movable partition 8. The rear end of the ampoule is sealed by the movable wall 9 which, thus, also seals the rear chamber 7. The two movable walls 8 and 9 can be moved forwards in the ampoule with sealing against the ampoule wall, said ampoule having a substantially circular-cylindrical shape for this purpose.

The front chamber 6 of the ampoule contains one or more medicaments 10 in dry state, preferably freeze-dried. In this form, also sensitive substances have a relatively good stability. The rear chamber 7 contains a liquid phase 11 which is intended to dissolve the dry injection substance. This liquid phase usually consists of water or a physiological saline solution, and such auxiliary substances as are usual in pharmacological practice can be added to it.

In the wall of the ampoule, connecting passage 12 in the form of a recess is arranged and extends substantially in the longitudinal direction of the ampoule. The overflow passage 12 is located such that it is completely in the front space 6 before the ampoule has been readied for injection and has such a length that it enables a flow past the movable wall 8.

Fig. 2 shows the injection device of the invention in an assembled state where it can be easily carried along by the patient. The device is generally shaped as a fountain-pen and consists of a front casing portion 13 which encloses a dual-chamber cylinder ampoule according to Fig. 1 for the agent to be injected, a rear casing portion 14 enclosing a mechanism for dosage and administration of the agent and a protective cap 15 over the injection needle. The mechanism for dosing and administering the agent is made in any one of several ways known per se and is not described here in greater detail. Usually it works in such a way that the control knob 16 at the rear end of the device is turned so that an index is set against a scale, a suitable dose being determined. In administration, the control knob is thereafter pushed in, whereby the set dose is administered through the needle. Many different embodiments of such a mechanism for dosage and administration are previously known and can be used in the injection device of the present invention.

Fig. 3 shows the injection device in its disassembled state. Here the protective cap 15 has also been removed so that the front portion 17 of the neddle with its holder means 18 is shown. The neddle can be screwed onto the front end of the front casing portion 13 by means of the holder device and can be easily replaced. The protective cap 15 should then be applied all the time so that sterility is maintained, and should not be removed until immediately before the injection. An aperture 19 is also made in the front casing portion 13 through which the user can easily control whether any ampoule is inserted and how much is left of the injection solution.

The rear casing portion 14 can be screwed into the front case portion 13 by means of the thread 20. Simultaneously with this screwing an inserted dual-chamber cylinder ampoule for injection is readied, as will be described more closely in the following.

Fig. 4 is a view partly in longitudinal section of the disassembled injection device according to Fig. 3. Here it is apparent that a dual-chamber cylinder ampoule of the type shown in Fig. 1 has been inserted into the front case portion 13 and moved so far that its membrane 3 has been uncovered to be penetrated by the neddle. In the rear case portion 14 the dosage and administration mechanism is schematically indicated at 22. This mechanism is provided with a forwardly directed operating rod 23. By its actuation the dual-chamber cylinder ampoule is first readied for injection and determined doses of the injection agent can thereafter be administered by the aid of the control knob 16.

The rear casing portion 14 can be screwed into the front case portion 13 by the external thread 20 engaging the internal thread 24.

Fig. 5 shows the device assembled and ready for injection. Here the rear movable wall 9 has been moved so far that it has got into contact with the front movable wall 8. This has been brought so far that it has got just opposite the connecting passage 12 and the liquid phase 11 has then flowed past the front movable wall 8 and been mixed with the dry medicament. The pointed rear end 21 of the neddle has also been introduced through the membrane 3. The two movable walls 8 and 9 are in contact with each other and have been moved so far that all air in the front space 6 has been expelled through the neddle. The device is now ready for injection.

The function of the device when being readied for injection is as follows :

In the rear casing portion 14, the operating rod 23 and the control knob 16 of the dosing and administering mechanism 22 is first set to a starting or zero position. This is done in a way as determined by the design of the mechanism known per se. The rear casing portion 14 is thereafter screwed into the front casing portion 13 until the operating rod 23 is resting lightly against the rear movable wall 9 in the dual-chambe cylinder ampoule.

When the rear case portion is screwed in further, the operating rod will push the rear movable wall 9 forwards in the cylinder ampoule, and as the liquid 11 in the rear space 7 is substantially incompressible, the front movable wall 8 will also be pressed forwards. A certain overpressure in the front chamber 6 will arise as air cannot escape.

When the front movable wall 8 has been pushed so far that it is just opposite the overflow passage 12 a liquid connection will be established between the front and the rear chambers. By the further forward motion of the rear movable wall 9 the liquid 11 will then be urged into the front chamber 6 through the overflow passage 12. At this stage, the front movable wall 8 will not move.

When all liquid has been urged into the front space, the rear movable wall 9 will get into mechanical contact with the front movable wall 8. The liquid will now dissolve the dry medicament 10 forming an injection solution ready for use. The holder 18 with the attached neddle 17 is thereafter screwed onto the front case portion 13, the membrane 3 of the cylinder ampoule being penetrated by the rear neddle tip 21, and the overpressure in the front chamber is released.

By pushing the control knob 16 fully home, the operating rod 23 is actuated so that the walls 9 and 8 are moved further forwards and air in the cylinder ampoule will exit through the neddle 17. The device is now ready for injection, as shown in Fig. 5.

When readying the device it is necessary to hold it vertically with the neddle end pointing upwards, and the screwing together must not be carried out too quickly. In this way the liquid will rise calmly through the dry substance dissolving it, and no vigorous mixing takes place. Such vigorous mixing is unsuitable for many sensitive substances as it may affect the substance.

It is a preferred embodiment that the dual-chamber cylinder ampoule 1 is positioned in the front casing portion 13 and the solid medicament is dissolved before the neddle 21 penetrates the membrane 3 of the ampoule. By the overpressure occuring, the tendency of foaming and formation of bubbles is reduced when the liquid and the solid material are mixed, which is less harmful to the medicament. However, for medicaments that are not so sensitive, the neddle holder 18 with the neddle can be screwed onto the front casing portion 13 before the cylinder ampoule is introduced and the two casing portions are screwed together. The rear tip of the neddle will then penetrate the membrane 3 before the solid substance and the liquid are mixed and no overpressure arises in the mixing chamber.

When the device is to be used for the administration of an injection the protective cap over the neddle is first taken off. The desired dose is thereafter set by means of the control knob 16 and by depressing the control knob the dose is administered through the neddle. Further doses can thereafter be administered as long as there is injection solution left in the cylinder ampoule. After each administration, the neddle is usually replaced with a new sterile neddle. This can easily be done by screwing off the holder device 18 with the attached neddle from the front end of the injection device and a new holder device with neddle is screwed on. At the same time the rear pointed end of the neddle will penetrate the membrane 3 and provide a liquid connection to the interior of the ampoule.

The varied embodiment of the device shown in Fig. 6 comprises a holder means in which the container 1 can be placed. The holder means consists of two substantially tubular members that can be screwed together, viz. a front tubular member 24 and a rear tubular member 28. The front tubular member 24 has a tapering recess 25 in its front end in which the neck ring 2 of the ampoule 1 can be received. At its rear end the front tubular member is provided with an internal thread 26 into which an external thread 27 on the rear tubular member 28 can be threaded. At its rear end the rear tubular member 28 has a closed rear wall 29 to which a fixed piston is attached internally in the rear tubular member 28 which piston has a diameter less than the inside diameter of the ampoule and extends towards the ampoule 1.

In preparation of the injection solution the rear tubular member 28 is threaded into the front tubular member 24, the holder means essentially being held vertically with the tapering recess 25 turned upwards. When the rear tubular member 28 is threaded into the front tubular member 24 the fixed piston 30 will move the rear tubular wall upwards compressing the liquid 11 in the rear room 7. The liquid will then exert a pressure on the front wall 8 so that this is moved upwards to a position right in front of the connecting passage 12, in which position the liquid 11 can flow calmly through the connecting passage 12 into the front space 6 and be mixed with the medicament substance 10. As the two tubular members 24 and 28 are screwed together a very calm flow of the liquid into the front space 6 will take place which, moreover, is closed by the membrane at the front end of the ampoule. When the liquid flows into the front space 6 a pressure above atmospheric is formed in this and a small pocket 31 with compressed gas is formed at the top of the ampoule, as is apparent from Fig. 7, which shows the holder means in the position when the two tubular members 24 and 28 are completely threaded into each other and all liquid has streamed into the front space 6. Thanks to the calm inflow of the liquid into the upper space 6 and the pressure above atmospheric formed foam formation in mixing is prevented. Of course the device can thereafter be turned a few times, if required, to dissolve the medicament substance completely in the liquid.

When taking out the injection solution prepared in this way the device is turned to the position shown in Fig. 8, thus with the front end of the ampoule 1 turned downwards, the gas in the front space 6 of the ampoule 1 being collected at the top and not close to the membrane. The injection solution can then be taken out by the aid of a cannula 32 which is introduced through the membrane and transferred to a usual hypodermic syringe 33 in known manner. It is easier to take out the injection solution from the ampoule 1 thanks to the pressure above atmospheric prevailing in the front space 6 of the ampoule so that the solution at least at the introductory moment will flow by its own pressure through the cannula 32 into the hypodermic syringe 33.

As previously mentioned a further varied embodiment of the device according to the invention is shown in Figs. 9-11 which, however, has substantially the same constituents as the device shown in Figs. 6 and 7. The main difference is that the device according to Figs. 9-11 is designed to be directly provided with a cannula at the tapering recess 25 of the front tubular member 24. Moreover, the rear wall 29 of the rear tubular member 28 is not closed but has a central hole 34 through which an operating rod 35 passes. The operating rod 35 is integrally connected with the piston 30 within the rear tubular member 28, the piston however not being attached to the rear tubular member 28 but restrictedly movable in its longitudinal direction by the aid of the operating rod 35. Like in the device shown in Figs. 6-8 the outside diameter of the

piston 30 is less than the inside diameter of the ampoule 1 but is at the same time larger than the diameter of the hole 34 in the rear wall 29 so that the piston 30 cannot be moved out of the rear tubular member 28. The two tubular members 24 and 28 are screwed together from the position shown in Fig. 9, in which the constituents of the injection solution are quite separated from one another, in the same way as described in connection with the first varied embodiment according to Figs. 6-8, until a complete mixture has been achieved and the device is in the position shown in Fig. 10. In this position a cover 36 is put onto the tapering recess 25 of the front tubular member 24. Moreover, a cannula 32 is attached to the cover 35 which penetrates the membrane of the ampoule 1 when the cover is put onto the tapering recess 25. This is done in a substantially vertical position with the recess 25 turned upwards. The device is then ready for use as a hypodermic syringe, the injection being carried out by pressing in the operating rod 35 so that the piston 30 moves the two movable walls 8 and 9 forwards in the front space 6 in the ampoule and the gas in the ampoule is first removed and so that thereafter the injection solution is fed out through the cannula 32 in known manner.

A very practical and simple instrument for preparation of an injection solution is obtained with the device of the invention. As mentioned above, the device provides a very calm safe mixture of the constituents of the injection solution. If mixing is carried out too quickly the result is particle formation and opalescence. Both are expressions of aggregation. The device is preferably made of a plastic material and in that case the costs of the manufacture of the device will be very low and the device can be used for non-recurrent use. The pitch of the threadable members is not critical but is preferably in the range of 0.5-10 mm.

The device of the invention is preferably used for subcutaneous injection but other injection methods according to current medical practice are also possible, for example intramuscular injection.

When the cylinder ampoule is emptied, the injection device is screwed apart and the empty ampoule is taken out. The dosing mechanism is set to zero and after this the device can be readied again for injection, as indicated above. The screwed-together and readied device can be easily carried along by the user in order to be used at suitable times.

It may be necessary to protect sensitive medicaments, especially of the polypeptide type, aginst mechanical action when they are in a dissolved form. The moments especially critical are the reconstitution of a dried powder, on one hand, and, on the other hand, the subsequent handling of the prepared solution. The latter will be perticularly important when multi-dose preparations are concerned, which must necessarily be handled a number of times.

The use of conventional packages and hypodermic syringes does not give any aid per se to protect against mechanical stresses which, however, this invention does. As the reconstitution of the dried powder by means of the invention is carried out in a very careful way determined by the design, the sensitive medicament is spared. As the solution is prepared at a certain overpressure, foaming and formation of bubbles are also prevented at this stage. The subsequent handling of the prepared solution will also be very gentle in the invention. Practically all air that has been in contact with the solution is removed as the injecting device is readied to give off a first injection from a newly inserted dual-chamber cylinder ampoule. In this way the interface is eliminated which in the handling of the container with solution gives rise to the negative effects on the sensitive medicament, and the container can thereafter be handled without special respect to the sensitive nature of the solution.

Thus it is possible by the present invention to prepare a solution to be used for a long or short time in a gentle way and to transport a prepared solution without degrading the quality of the sensitive medicament due to mechanical stress. Therefore the invention makes it possible that also sensitive medicaments can be made available for a comfortable ambulatory treatment.

The medicaments that can be used in the present device can consist of any substance or mixture of substances used in the previously known dual-chamber ampoules or which are suitable for this use. However, sensitive substances that cannot be stored for a long time in solution and which also have a tendency to be altered when dissolved are especially suitable. Examples of such substances are various polypeptides such as hormones and interferon. The invention has been found to be particularly suitable in the preparation and injection of solutions of growth hormones. These are very sensitive and are easily modified when a solution of them is prepared. By using the present invention in this case, such an influence is considerably reduced. This is extremely surprising and not predictable by one skilled in the art.

The dry medicaments are usually present in a freeze-dried or lyophilized state before the preparation of the injection solution. The liquid used for the solution usually consists of water to which agents for adjusting the osmotic pressure, preservatives, etc. have often been added in accordance with current pharmacological practice. It is also possible that the liquid phase itself can contain dissolved substances having a pharmacological effect which is then exerted together with the effect of the agent that is later dissolved in the liquid.

Another embodiment is that the liquid can consist of an injectable fat emulsion, for example such a one as is described in US patents 4073943 and 4168308. In this case the dry injection substance contains a wa-

ter-soluble or hydrophilic agent which is dissolved or dispersed in the aqueous phase of the emulsion in the mixture.

The injection device is made of some suitable material such as metal, for example stainless steel or light metal or some suitable plastic material. The choice of material is well within the competence of one skilled in the art.

Moreover, it should be noted that the method and device of the invention shown in the drawing and the detailed description are only an example and that other embodiments are also possible within the scope of the claims.

Claims

1. A method of preparing a solution, emulsion or suspension in water of one or more sensitive medicaments for one or more subsequent injections using a multi-chamber cylinder ampoule (1) known per se and comprising a front space (6) containing the sensitive medicament (10) and sealed at its front end by means of a membrane (3) penetrable to an injection needle (17) and delimited at its rear end by a front movable wall (8), a rear space (7) containing an aqueous phase (11) and delimited at its front end by the front movable wall (8) and delimited at its rear end by a rear movable wall (9), and a connecting passage (12) arranged in the wall of the ampoule between the rear and the front spaces, said rear movable wall (9) being moved forwards and entraining thereby the aqueous phase (11) and the front movable wall (8) until this is just opposite the connecting passage (12), so that the aqueous phase (11) upon continued displacement of the rear movable wall (9) will flow past the front movable wall into the front space and dissolve, suspend or emulsify the medicament (10), **characterized** in that the rear, movable wall (9) by means of a screw mechanism is pushed forward into the ampoule while the ampoule is held in essentially vertical direction with the needle end pointing upwards so that the aqueous phase (11) is made to flow calmly from below and upwards through the medicament (10) avoiding any shaking and admixture of air.

2. The method of claim 1, **characterized** in that the aqueous phase (11) and the medicament (10) are brought into contact with one another at a pressure above atmospheric.

3. The method of claim 1 or 2, **characterized** in that the injection neddle (17) is made to penetrate the membrane (13) only after the medicament (10) has been dissolved, emulsified or suspended in the aqueous phase (11).

4. A device for the preparation of an injection solution of degradation-sensitive substances and a subsequent injection of this solution, said device comprising :

a) a container (1) for the constituents of the injection solution, in which the constituents are kept separated but can be brought together by external action to be mixed and dissolved and which is made as a tube (1) which is sealed at its front end by means of a penetrable membrane (3), in a space (6) between the penetrable membrane and a front movable wall (8) contains the solid constituents (10) of the injection solution, in a space (7) between the front movable wall (8) and a rear movable wall (9) contains the liquid constituents (11) of the injection solution and in the tubular wall is provided with a connecting passage (12) so arranged that when the rear movable wall (9) is moved forwards together with the liquid (11) and the front movable wall (8), the liquid can flow past the front movable wall (8) and be mixed with the solid constituents (10) to a solution ;

b) holder means in which the container (1) can be fixed such that the constituents of the injection solution are brought together and mixed and which is made of two tubular members (13, 14) which can be screwed together and enclose the container (1) such that when the members are screwed together the front end of the container with the penetrable membrane (3) is exposed at the front end of the holder means to be penetrated by an injection neddle (17, 21) and at the rear end of the container, the rear movable wall (9) is moved forwards together with the liquid (11) and the front movable wall (8) so that the liquid (11) is made to flow through the connecting passage (12) over to the space of the solid constituents (6) to be mixed with these to a solution ;

c) holder means (18) for an injection neddle (17) arranged to be applied to the front end of the holder means (13) of the container so that the neddle (21) can be connected with the interior (6) of the container through the penetrable membrane (3) ; and

d) a dosing device (22) connected to the holder means (13, 14) of the container, through the operation of which the rear movable wall (9) in the container is made to be displaced forwards in a controlled way administering determined doses of the injection solution, said dosage device (22) being brought to a starting position for dosage when screwed together with the holder means (13, 14) of the container.

5. A device for preparation of an injection solution of substances sensitive to degradation, the consitutents of the injection solution are kept in a container (1) in which the constituents are separated but can be brought together to be mixed and dissolved through external influence and which is made as a container (1) which is sealed at its front end (2) by means of a penetrable membrane, contains in a space (6) between the penetrable membrane and a front movable

wall (8) the solid constituents (10) of the injection solution, contains in a space (7) between the front movable wall (8) and a rear movable wall (9) the liquid constituents (11) of the injection solution and is provided in the tubular wall with a connecting passage (12) so arranged that when the rear movable wall (9) is moved forwards together with the liquid (11) and the front movable wall (8), the liquid (11) can stream past the front movable wall (8) and be mixed with the solid constituents (10) to a solution, characterised in that the device comprises a holder means (24, 28) in which the container can be fixed so that the consituents (10, 11) of the injection solution can be brought together and mixed, and which is made of two tubular members (24, 28) which can be screwed together and enclose the container (1) so that when the members (24, 28) are screwed together the front end (2) of the container (1) with the penetrable membrane is exposed at the front end (25) of the holder means and at the rear end of the container (1) the rear tubular wall (9) is moved forwards together with the liquid (11) and the front movable wall (8) by means of a piston (30) arranged at the rear end (28) of the holder means pressing the rear movable wall (9) of the container (1) forwards so that the liquid (11) can be brought to stream through the connecting passage (12) over to the space (6) of the solid constituents (10) and be mixed with these to a solution.

6. The device of claim 5, **characterized** in that the piston (30) is fixedly arranged at the rear end (28) of the holder means and that the front tubular member (24) of the holder means is provided with an opening straight in front of the penetrable membrane of the container so that a cannula (32) can be introduced through the opening and the penetrable membrane for taking out a prepared injection solution for an hypodermic syringe (33).

7. The device of claim 5, **characterized** in that the piston (30) is provided with an operating rod (35) which projects through a rear wall (29) at the rear end (28) of the holder means and that an attachment (36) of an injection cannula (32) is arranged at the front end (25) of the holder means which can be adapted to the holder means (24, 25) and then penetrate the membrane of the container (1).

Patentansprüche

1. Verfahren zur Herstellung einer wäßrigen Lösung, Emulsion oder Suspension eines empfindlichen Medikaments oder mehrerer für eine Injektion oder mehrere aufeinander folgende Injektionen unter Verwendung einer an sich bekannten, eine Vielzahl von Kammern aufweisenden zylindrischen Ampulle (1), die einen vorderen Raum (6), der das empfindliche Medikament (10) enthält und an seinem vorderen Ende mittels einer durch eine Injektionsnadel (17) durchstoßbare Membran (3) verschlossen und an seinem hinteren Ende durch eine nach vorne bewegbare Wandung (8) begrenzt ist, die einen hinteren, eine wäßrige Phase (11) enthaltenden Raum (7), der an seinem vorderen Ende durch die vordere, bewegliche Wandung (8) und an seinem hinteren Ende durch eine hintere, bewegliche Wandung (9) begrenzt ist, und die einen in der Wandung der Ampulle zwischen den hinteren und vorderen Räumen angeordneten Verbindungskanal (12) umfaßt, wobei die hintere, bewegliche Wandung (9) nach vorne bewegbar ist und dabei die wäßrige Phase (11) und die vordere, bewegliche Wandung (8) mitnimmt, bis sich diese gerade gegenüber dem Verbindungskanal (12) befindet, so daß die wäßrige Phase (11) bei fortgesetzter Verschiebung der hinteren, beweglichen Wandung (9) an der vorderen, beweglichen Wandung vorbei in den vorderen Raum strömt und das Medikament (10) löst, suspendiert oder emulgiert, dadurch gekennzeichnet, daß die hintere, bewegliche Wandung (9) mittels eines Schraubenmechanismus nach vorne in die Ampulle geschoben wird, während die Ampulle in im wesentlichen vertikaler Ausrichtung mit nach oben weisendem Kanülenende gehalten wird, so daß die wäßrige Phase (11) allmählich bzw. ohne Störung von unten und nach oben durch das Medikament (10) unter Vermeidung jeglichen Schüttelns und der Zumischung von Luft strömen kann.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die wäßrige Phase (11) und das Medikament (10) bei einem Druck oberhalb des atmosphärischen Druckes in Kontakt zueinander gebracht werden.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Injektionsnadel (17) so ausgebildet ist, daß sie die Membran (13) lediglich dann durchstößt, wenn das Medikament (10) in der wäßrigen Phase (11) gelöst, emulgiert oder suspendiert ist.

4. Vorrichtung für die Herstellung einer Injektionslösung von zersetzungsempfindlichen Substanzen und für eine nachfolgende Injektion dieser Lösung, die

a) einen Behälter (1) für die Bestandteile der Injektionslösung, in dem die Bestandteile getrennt gehalten, aber zum Mischen und Lösen durch äußere Einwirkung zusammengebracht werden können, wobei der Behälter als Röhre (1) ausgebildet ist, die an ihrem vorderen Ende mittels einer durchstoßbaren Membran (3) verschlossen ist, in einem Raum (6) zwischen der durchstoßbaren Membran und einer vorderen, beweglichen Wandung (8) die festen Bestandteile (10) der Injektionslösung enthält, in einem Raum (7) zwischen der vorderen, beweglichen Wandung (8) und einer hinteren, beweglichen Wandung (9) die flüssigen Bestandteile (11) der Injektionslösung enthält und in der Rohrwandung mit einem Verbindungskanal (12) versehen ist,

wobei der Verbindungskanal so angeordnet ist, daß bei Vorwärtsbewegung der hinteren, beweglichen Wandung (9) zusammen mit der Flüssigkeit (11) und der vorderen, beweglichen Wandung (8) die Flüssigkeit an der vorderen, beweglichen Wandung (8) vorbeiströmen und mit den festen Bestandteilen (10) zu einer Lösung vermischt werden kann ;

b) Halteeinrichtungen, in denen der Behälter (1) zu Zusammenbringen und Mischen der Bestandteile der Injektionslösung fixiert werden kann, die von zwei zusammenschraubbaren und den Behälter (1) verschließenden, rohrförmigen Teilen (13, 14) gebildet werden, so daß beim Zusammenschrauben der Teile das vordere Ende des Behälters mit der durchstoßbaren Membran (3) an dem vorderen Ende der von einer Injektionsnadel (17, 21) zu durchstoßenden Halteeinrichtungen angeordnet ist und an dem hinteren Ende des Behälters die hintere, bewegliche Wandung (9) zusammen mit der Flüssigkeit (11) und der vorderen, beweglichen Wandung (8) nach vorne bewegt wird, damit die Flüssigkeit (11) durch den Verbindungskanal (12) in den Raum der festen Bestandteile (6) strömt, um mit diesen zu einer Lösung vermischt zu werden ;

c) Halteeinrichtungen (18) für eine Injektionsnadel (17), die zum Anbringen am vorderen Ende der Halteeinrichtungen (13) des Behälters angeordnet sind, so daß die Nadel (21) mit dem Inneren (6) des Behälters durch die durchstoßbare Membran (3) verbunden werden kann ; und

d) eine Dosiereinrichtung (22), die mit den Halteeinrichtungen (13, 14) des Behälters verbunden ist und durch deren Betätigung die hintere, bewegliche Wandung (9) in dem Behälter in kontrollierter Weise unter Verabreichung bestimmter Dosen der Injektionslösung nach vorne verschiebbar ist, wobei die Dosiereinrichtung (22) in eine Startposition für die Dosierung gebracht wird, wenn sie mit den Halteeinrichtungen (13, 14) des Behälters zusammengeschraubt wird, umfaßt.

5. Vorrichtung für die Herstellung einer Injektionslösung von zersetzungsempfindlichen Substanzen, bei der die Bestandteile der Injektionslösung in einem Behälter (1) gehalten werden, in dem die Bestandteile getrennt sind, aber zum Mischen und Lösen durch äußere Einwirkung zusammengebracht werden können, und die als Behälter (1) ausgebildet ist, der an seinem vorderen Ende (2) mit Hilfe einer durchstoßbaren Membran verschlossen ist, der in einem Raum (6) zwischen der durchstoßbaren Membran und einer vorderen, beweglichen Wandung (8) die festen Bestandteile (10) der Injektionslösung enthält, der in einem Raum (7) zwischen der vorderen, beweglichen Wandung (8) und einer hinteren, beweglichen Wandung (9) die flüssigen Bestandteile (11) der Injektionslösung enthält und der in der rohrförmigen Wandung mit einem Verbindungskanal (12) versehen ist, welcher so angeordnet ist, daß bei Vorwärtsbewegung der hinteren, beweglichen Wandung (9) zusammen mit der Flüssigkeit (11) und der vorderen, beweglichen Wandung (8) die Flüssigkeit (11) an der vorderen, beweglichen Wandung (8) vorbeiströmen und mit den festen Bestandteilen (10) zu einer Lösung vermischt werden kann, dadurch gekennzeichnet, daß die Vorrichtung Halteeinrichtungen (24, 28) umfaßt, in denen der Behälter zum Zusammenbringen und Vermischen der Bestandteile (10, 11) der Injektionslösung befestigbar ist und die aus zwei zusammenschraubbaren und den Behälter (1) einschließenden, rohrförmigen Teilen (24, 28) besteht, so daß beim Zusammenschrauben der Teile (24, 28) das vordere Ende (2) des Behälters (1) mit der durchstoßbaren Membran an dem vorderen Ende (25) der Halteeinrichtung angeordnet ist und am hinteren Ende des Behälters (1) die hintere, rohrförmige Wandung (9) zusammen mit der Flüssigkeit (11) und der vorderen, beweglichen Wandung (8) mittels eines an dem hinteren Ende (28) der Halteeinrichtungen angebrachten Kolbens (30) nach vorne bewegbar ist, wobei die hintere, bewegliche Wandung (9) des Behälters (1) nach vorne gedrückt wird, so daß die Flüssigkeit (11) durch den Verbindungskanal (12) in den Raum (6) für die festen Bestandteile (10) strömt und mit diesen zu einer Lösung vermischt wird.

6. Vorrichtung nach Anspruch 5, dadurch gekennzeichnet, daß der Kolben (30) starr an dem hinteren Ende (28) der Halteeinrichtungen befestigt ist und daß das vordere rohrförmige Teil (24) der Halteeinrichtungen direkt vor der durchstoßbaren Membran des Behälters mit einer Öffnung versehen ist, so daß eine Kanüle (32) zur Einführung durch die Öffnung und die durchstoßbare Membran zur Entnahme einer vorbereiteten Lösung für eine subkutane Injektionsspritze eingeführt werden kann.

7. Vorrichtung nach Anspruch 5, dadurch gekennzeichnet, daß der Kolben (30) mit einer Stange (35) versehen ist, die durch eine hintere Wandung (29) am hinteren Ende (28) der Halteeinrichtungen ragt, und daß an dem vorderen Ende (25) der Halteeinrichtungen eine Befestigungseinrichtung (36) einer Injektionskanüle (32) angebracht ist, die an die Halteeinrichtungen (24, 25) anpaßbar ist und anschließend die Membran des Behälters (1) durchstößt.

Revendications

1. Procédé de préparation d'une solution, émulsion ou suspension dans l'eau d'un ou plusieurs médicaments sensibles pour une ou plusieurs injections subséquentes en utilisant une ampoule cylindrique à chambre multiple (1) connue per se et comprenant un

espace avant (6) contenant le médicament sensible (10) et obturée de façon étanche sur son extrémité avant au moyen d'une membrane (3) pénétrable par une aiguille d'injection (17) et délimitée sur son extrémité arrière par une paroi mobile avant (8), un espace arrière (7) contenant une phase aqueuse (11) et délimité sur son extrémité avant par la paroi mobile avant (8) et délimité sur son extrémité arrière par une paroi mobile arrière (9), et un passage de communication (12) disposé dans la paroi de l'ampoule entre les espaces arrière et avant, la paroi mobile arrière (9) étant déplacée sur l'avant et entraînant ainsi la phase aqueuse (11) et la paroi mobile avant (8) jusqu'à ce que celle-ci se situe juste en regard du passage de communication (12), de sorte que la phase aqueuse (11) lorsque le déplacement de la paroi mobile arrière (9) se poursuit s'écoulera au-delà de la paroi mobile avant jusque dans l'espace avant et dissoudra, mettra en suspension ou en émulsion le médicament (10), caractérisé en ce que la paroi mobile arrière (9) est poussée sur l'avant au moyen d'un mécanisme à vis jusque dans l'ampoule tandis que l'ampoule est maintenue sensiblement dans la direction verticale avec la pointe de l'aiguille dirigée vers le haut de sorte que la phase aqueuse (11) peut s'écouler doucement à partir du bas et vers le haut à travers le médicament (10) en évitant toute agitation et addition d'air.

2. Dispositif selon la revendication 1, caractérisé en ce que la phase aqueuse (11) et le médicament (10) sont mis en contact l'un avec l'autre à une pression au-dessus de la pression atmosphérique.

3. Procédé selon la revendication 1 ou 2, caractérisé en ce que l'on fait pénétrer l'aiguille d'injection (17) dans la membrane (13) uniquement après que le médicament (10) a été dissous, émulsifié ou mis en suspension dans la phase aqueuse (11).

4. Dispositif pour la préparation d'une solution d'injection de substances sensibles à la dégradation et une injection subséquente de cette solution, le dispositif comprenant :

a) un conteneur ou récipient destiné aux éléments constitutifs de la solution d'injection dans laquelle les éléments constitutifs sont maintenus séparés mais peuvent être combinés par une action externe pour être mélangé et dissous, et qui se présente sous la forme d'un tube qui est obturé de façon étanche sur son extrémité avant au moyen d'une membrane pénétrable dans un espace situé entre la paroi pénétrable et une paroi mobile avant contient les éléments constitutifs solides de la solution d'injection, dans un espace situé entre la paroi mobile avant et une paroi mobile arrière contient les constituants du liquide de la solution d'injection et un passage de communication est prévu dans la paroi tubulaire de façon que lorsque la paroi mobile arrière est déplacée vers l'avant conjointement avec le liquide et la partie mobile avant, le liquide peut s'écouler au-delà de la paroi mobile avant et être mélangé avec les éléments constitutifs solides à la solution ;

b) Support dans lequel on peut fixer le conteneur ou récipient de telle manière que les éléments constitutifs de la solution d'injection puissent être regroupés et mélangés et qui est constitué de deux parties tubulaires pouvant être vissées ensemble et qui renferment le conteneur de telle façon que lorsque les parties sont vissés ensemble l'extrémité avant du conteneur avec la membrane pénétrable est exposée sur le côté avant de l'élément de support afin d'être transpercée par une aiguille d'injection et la paroi mobile arrière sur l'extrémité arrière du conteneur est déplacée vers l'avant conjointement avec le liquide et la paroi mobile avant de telle façon que le liquide puisse s'écouler par le passage de communication jusqu'à l'espace des éléments constitutifs solides à mélanger avec ceux-ci à une solution ;

c) Support pour une aiguille d'injection disposé de façon à pouvoir être appliqué sur l'extrémité avant de l'élément de support pour une aiguille d'injection disposée de façon à pouvoir être appliquée sur l'extrémité avant de l'élément de support du conteneur de sorte que l'aiguille peut être raccordée avec l'intérieur du conteneur à travers la membrane pénétrable ; et

d) un dispositif de dosage raccordé au support du conteneur, grâce au fonctionnement duquel la paroi mobile arrière dans le conteneur peut être déplacée vers l'avant d'une manière contrôlée pour administrer des doses déterminées de la solution d'injection, ce dispositif de dosage étant amené sur une position de départ pour le dosage lorsque les parties de support du conteneur sont vissées ensemble.

5. Dispositif pour la préparation d'une solution d'injection de substances sensibles à la dégradation, les éléments constitutifs de la solution d'injection étant maintenus dans un conteneur ou récipient (1) dans lequel les éléments constitutifs sont séparés mais peuvent être mis ensemble pour être mélangés et dissous par influence extérieure et qui est réalisé sous forme d'un conteneur ou récipient (1) rendu étanche sur son extrémité avant (2) au moyen d'une membrane pénétrable, contenant dans un espace (6) entre la membrane pénétrable et une paroi mobile avant (8) les éléments constitutifs solides (10) de la solution d'injection, et contenant dans un espace (7) entre la paroi mobile avant (8) et une paroi mobile arrière (9) les éléments constitutifs liquides (11) de la solution d'injection et qui est muni dans la paroi tubulaire d'un passage de communication (12) disposé de telle manière que lorsque la paroi mobile arrière (9) est déplacée vers l'avant avec le liquide (11) et la paroi mobile avant (8), le liquide (11) peut s'écouler

au-delà de la paroi mobile avant (8) et être mélangé avec les éléments constitutifs solides (10) à une solution, caractérisé en ce que le dispositif comprend des parties de support (24, 28) dans lesquels on peut fixer le conteneur de sorte que les éléments constitutifs (10, 11) de la solution d'injection peuvent être mis ensemble et mélangés, et qui est réalisé à partir de deux parties tubulaires (24, 28) qui peuvent être vissées ensemble et renferment le conteneur (1) de sorte que lorsque les parties (24, 28) sont vissées l'extrémité avant (2) du conteneur avec la membrane pénétrable est exposée sur l'extrémité avant (25) de l'élément de support et sur l'extrémité arrière du conteneur (1) la paroi tubulaire arrière (9) est déplacée vers l'avant avec le liquide (11) et la paroi mobile avant (8) au moyen d'un piston (30) disposé sur l'extrémité arrière (28) des éléments de support appuyant contre la paroi mobile arrière (9) du conteneur (1) sur l'avant de sorte que le liquide (11) peut s'écouler par le passage de communication (12) jusqu'à l'espace (6) des éléments constitutifs solides (10) et être mélangé avec ceux-ci à une solution.

6. Dispositif selon la revendication 5, caractérisé en ce que le piston (30) est disposé à demeure sur l'extrémité arrière (28) de l'élément de support et en ce que l'élément tubulaire avant (24) du support est muni d'une ouverture juste en face de la membrane pénétrable du conteneur de sorte qu'une canule (32) peut être introduite par l'ouverture et la membrane pénétrable pour prélever une solution d'injection préparée pour une seringue hypodermique (33).

7. Dispositif selon la revendication 5, caractérisé en ce que le piston (30) est muni d'une tige d'actionnement (35) qui fait saillie à travers une paroi arrière (29) sur l'extrémité arrière (28) du support et en ce qu'une fixation (36) d'une canule d'injection (32) est disposée sur l'extrémité avant (25) du support qui peut être adapté aux éléments de support (24, 25) et pénètre alors dans la membrane du conteneur (1).

FIG.1

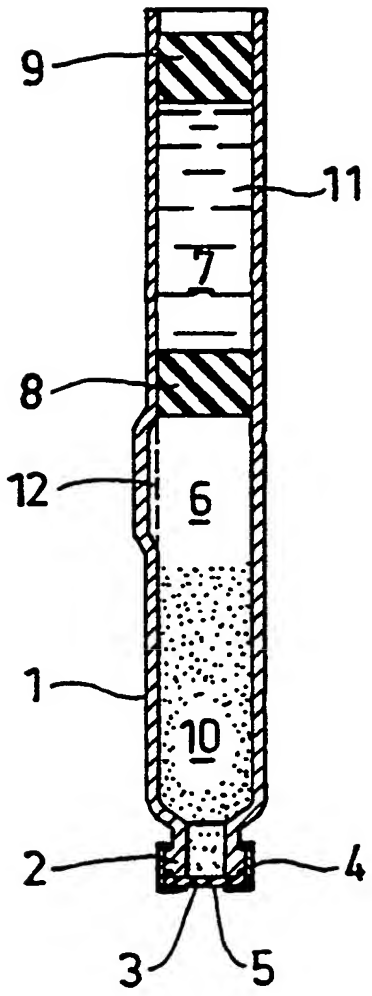

FIG.4

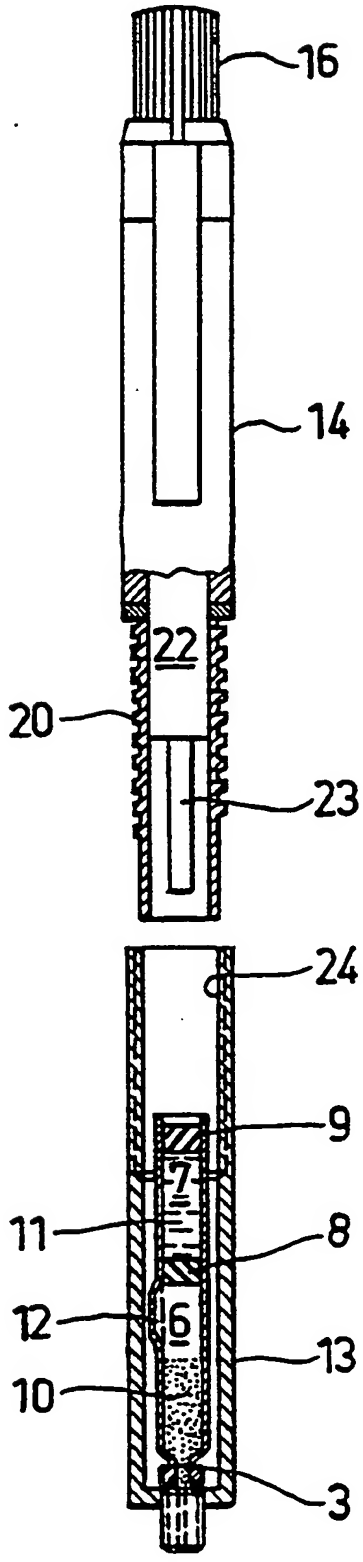

FIG.2

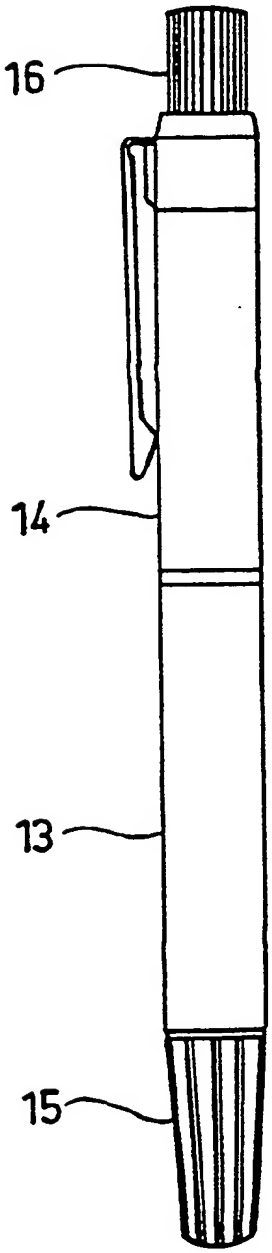

FIG.3

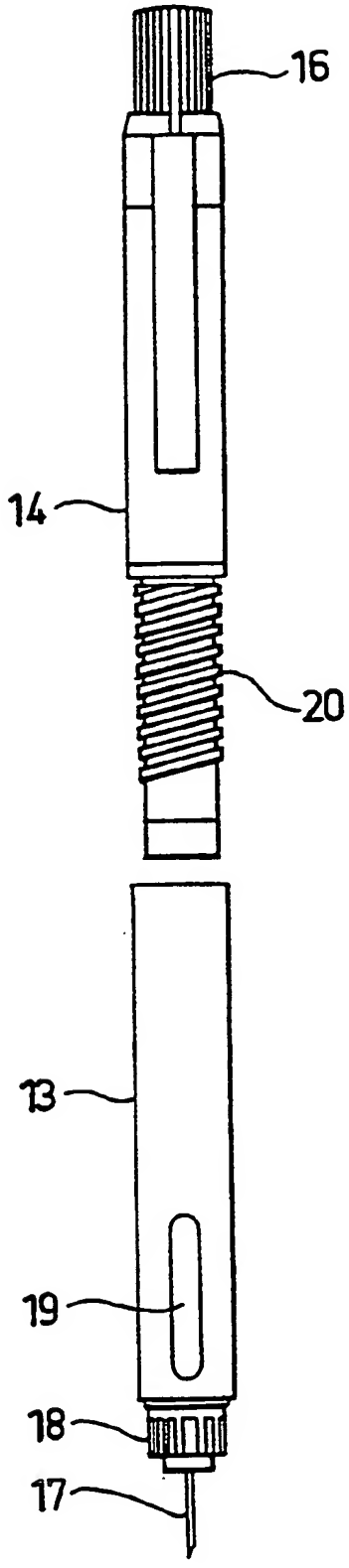

FIG.5

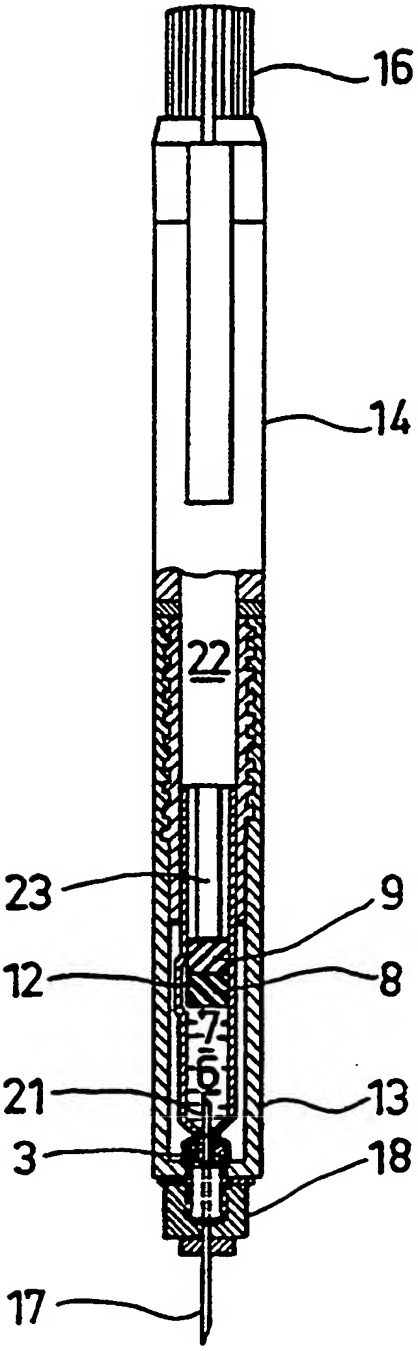

FIG. 6

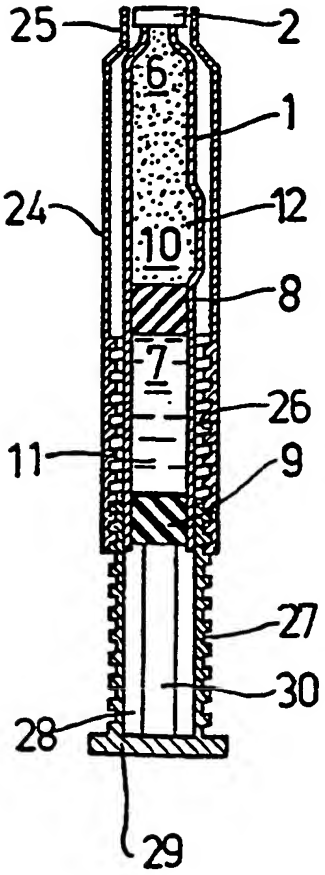

FIG. 7

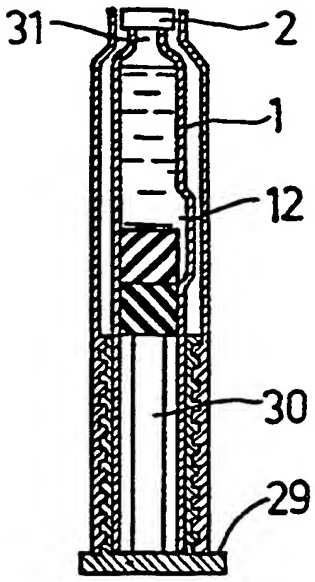

FIG. 8

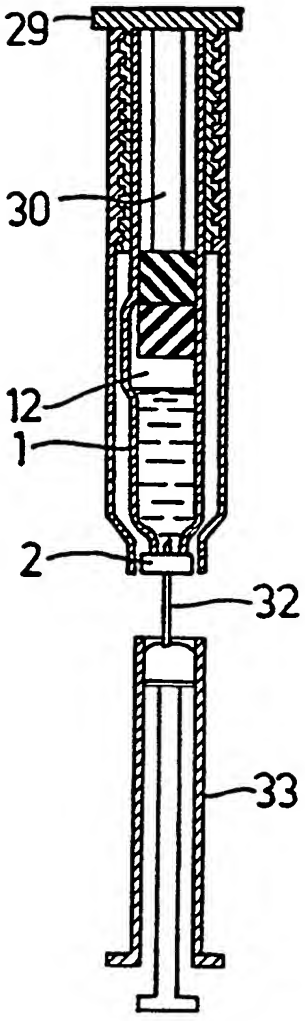

FIG.9

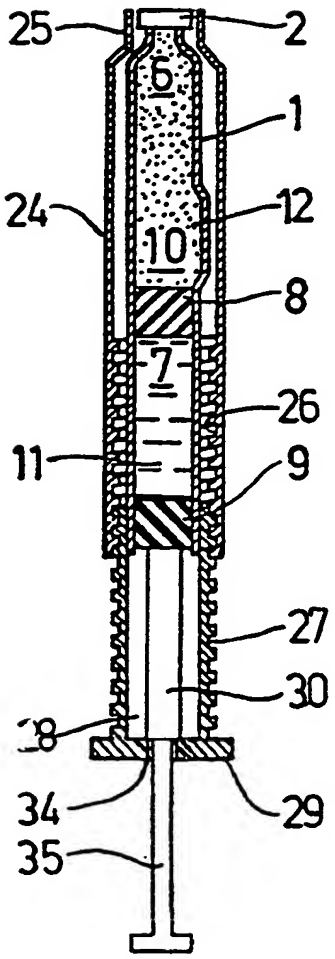

FIG.10

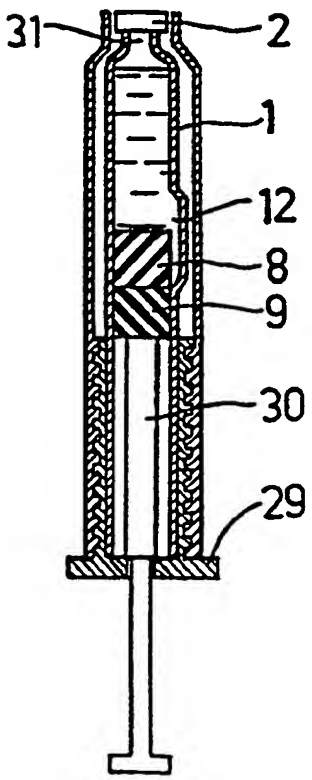

FIG.11